CLAIMS

1. A chimeric binding protein that is immunogenic in an animal, said chimeric binding protein being one that binds specifically to a first receptor, said first receptor being one that binds a second receptor present in an antigen of said animal, wherein said chimeric binding protein comprises:
- a B-cell epitope in the form of a binding site that specifically binds the first receptor and which competes with the second receptor for binding to the first receptor,
- a scaffold protein structure that stabilises the 3D conformation of the binding site, said scaffold protein structure being autologous in said mammal, and
- at least one tolerance breaking amino acid sequence, which is heterologous in said animal and which binds to an MHC Class II molecule in said animal.

2. The chimeric binding protein according to claim 1, wherein said scaffold protein structure is derived from an abundant protein, preferably an abundant serum protein.

3. The chimeric binding protein according to claim 1 or 2 wherein said scaffold protein structure is derived from albumin, an immunoglobulin, transferrin, and α_2-macroglobulin.

4. The chimeric binding protein of any one of claims 1-3, wherein said scaffold protein structure is derived from IgG.

5. The chimeric binding protein of any one of claims 1-4, wherein said scaffold protein structure is derived from the non-idiotypic region of a molecule selected from the group consisting of a complete antibody and a fragment thereof such as an F(ab')2 fragment, an Fab fragment, and an scFv.

6. The chimeric binding protein of any one of claims 1-5, wherein said scaffold protein structure comprises a substantially complete amino acid sequence of a polypeptide autologous in said animal.

7. The chimeric binding protein of any one of claims 1-6, wherein said scaffold protein structure comprises a substantial number of B-cell epitopes found in the autologous scaffold protein structure in the animal.

8. The chimeric binding protein of any one of claims 1-7, wherein said scaffold protein structure has substantially the same tertiary structure of a polypeptide autologous in said animal.

9. The chimeric binding protein of any one of claims 1-8, wherein said B-cell epitope is constituted by the idiotype of an antibody.

10. The chimeric binding protein of any one of claims 1-9, wherein said first receptor is the idiotype of an antibody or a specific binding region of a ligand that binds the second receptor in said animal.

11. The chimeric binding protein of any one of claims 1-10, wherein said first receptor is the idiotype of a monoclonal antibody.

12. The chimeric binding protein of any one of claims 1-11, wherein said tolerance breaking amino acid sequence is introduced by means of amino acid insertion or substitution in the amino acid sequence of the scaffold protein structure.

13. The chimeric binding protein of any one of claims 1-12, wherein the animal is a human being.

14. The chimeric binding protein of any one of claims 1-13, which is an anti-idiotypic antibody or an effectively binding fragment thereof that is modified so as to include said tolerance breaking amino acid sequence.

15. The chimeric binding protein of any one of claims 1-14, wherein the antigen of said animal that includes said second receptor is selected from the group consisting of immunoglobulin E, CD20, CD11a, beta amyloid, HER-2, and TNFα.

16. The chimeric binding protein of any one of claims 1-15, which further comprises
- at least one first moiety which effects targeting of the chimeric binding protein to an antigen presenting cell (APC) or a B-lymphocyte, and/or
- at least one second moiety which stimulates the immune system, and/or
- at least one third moiety which optimises presentation of the chimeric binding protein to the immune system.

17. The chimeric binding protein according to claim 16, wherein the tolerance breaking amino acid sequence and/or the first and/or the second and/or the third moiety is/are present in the chimeric binding protein by being bound to suitable side groups in the scaffold protein structure.

18. The chimeric binding protein according to claim 17, wherein the tolerance breaking amino acid sequence and/or the first and/or the second and/or the third moiety is/are present in the scaffold protein structure by means of at least one amino acid substitution and/or deletion and/or insertion and/or addition.

19. The chimeric binding protein according to any one of claims 1-18, wherein the tolerance breaking amino acid sequence is promiscuous in the animal species to which said animal belongs.

20. The chimeric binding protein according to any one of claims 1-19, wherein the tolerance breading amino acid sequence is selected from a natural promiscuous T helper cell epitope and an artificial MHC-II binding peptide sequence.

21. The chimeric binding protein according to claim 20, wherein the natural T-cell epitope is selected from a Tetanus toxoid epitope such as P2 or P30, a diphtheria toxoid epitope, an influenza virus hemagluttinin epitope, and a P. falciparum CS epitope, and wherein the artificial MHC-II binding peptide sequence is a PADRE peptide.

22. The chimeric binding protein according to any one of claims 16-21, wherein the first moiety is a substantially specific binding partner for a B-lymphocyte specific surface antigen or for an APC specific surface antigen, such as a hapten or a carbohydrate for which there is a receptor on the B-lymphocyte or the APC.

23. The chimeric binding protein according to any one of claims 16-22, wherein the second moiety is selected from a cytokine and a heat-shock protein.

24. The chimeric binding protein according to claim 23, wherein the cytokine is selected from, or is an effective part of, interferon γ (IFN-γ), Flt3L, interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 12 (IL-12), interleukin 13 (IL-13), interleukin 15 (IL-15), and granulocyte-macrophage colony stimulating factor (GM-CSF), and the heat-shock protein is selected from, or is an effective part of any of, HSP70, HSP90, HSC70, GRP94, and calreticulin (CRT).

25. The chimeric binding protein according to any one of claims 16-24, wherein the third moiety is of lipid nature, such as a palmitoyl group, a myristyl group, a farnesyl group, a geranyl-geranyl group, a GPI-anchor, and an N-acyl diglyceride group.

26. A nucleic acid fragment that encodes the chimeric binding protein according to any one of claims 1-25, or a nucleic acid fragment complementary thereto.

27. A vector carrying the nucleic acid fragment according to claim 26, such as a vector that is capable of autonomous replication.

28. The vector according to claim 27, which is selected from the group consisting of a plasmid, a phage, a cosmid, a mini-chromosome, and a virus.

29. The vector according to claim 27 or 28, comprising, in the 5'→3' direction and in operable linkage, a promoter for driving expression of the nucleic acid fragment according to claim 26, optionally a nucleic acid sequence encoding a leader peptide enabling secretion of or integration into the membrane of the polypeptide fragment, the nucleic acid fragment according to claim 26, and optionally a terminator.

30. The vector according to any one of claims 27-29 which, when introduced into a host cell, is capable or incapable of being integrated in the host cell genome.

31. The vector according to any one of claims 27-30, wherein a promoter drives expression in a eukaryotic cell and/or in a prokaryotic cell.

32. A transformed cell carrying the vector of any one of claims 27-30, such as a transformed cell which is capable of replicating the nucleic acid fragment according to claim 26.

33. The transformed cell according to claim 32, which is a microorganism selected from a bacterium, a yeast, a protozoan, or a cell derived from a multicellular organism selected from a fungus, an insect cell such as an S2 or an SF cell, a plant cell, and a mammalian cell.

34. The transformed cell according to claim 32-33, which expresses the nucleic acid fragment defined in claim 26, such as a transformed cell, which secretes or carries on its surface, the chimeric binding protein defined in any one of claims 1-25.

35. A composition for inducing production of antibodies against an antigen in the autologous host, the composition comprising

- a chimeric binding protein according to any one of claims 1-25, and
- a pharmaceutically and immunologically acceptable carrier and/or vehicle and/or adjuvant

36. A composition for inducing production of antibodies against an antigen in the autologous host, the composition comprising
- a nucleic acid fragment according to claim 26 or a vector according to any one of claims 27-31, and
- a pharmaceutically and immunologically acceptable carrier and/or vehicle and/or adjuvant.

37. A stable cell line which carries the vector according to any one of claims 27-31 and which expresses the nucleic acid fragment according to claim 26, and which optionally secretes or carries the chimeric binding protein according to any one of claims 1-25 on its surface.

38. A method for the preparation of the cell according to any one of claims 32-34, the method comprising transforming a host cell with the nucleic acid fragment according to claim 26 or with the vector according to any one of claims 27-31.

39. A method for preparing the chimeric binding protein of any one of claims 1-25, the method comprising the following steps:
1) providing a first molecule, which binds to a self-antigen of interest in an animal and which includes the first receptor,
2) immunizing, with the first molecule optionally being coupled to an immunogenic carrier, a transgenic animal that produces antibodies that are autologous in the animal harbouring the self-antigen or that are autologous in the animal harbouring the self-antigen except for the fact that they also include at least one amino acid sequence that breaks tolerance in the animal,
3) preparing and isolating hybridomas that produce antibodies that bind the first molecule,
4) screening the hybridomas of step 3 for their ability to produce antibodies that selectively bind to said first receptor, and
5) transforming a suitable host cell with at least genetic material that encodes antibodies or functional parts thereof where the genetic material is or can be isolated from the hybridomas of step 4 that produce selectively binding antibodies,
6) culturing the host cells transformed in step 5 under conditions that facilitate production of at least the antibodies or functional fragments thereof, and recovering the antibodies or functional fragments thereof from the host cell culture.

40. A method for preparing the chimeric binding protein of any one of claims 1-25, the method comprising the following steps:
1) providing a first molecule, which binds to a self-antigen of interest in an animal and which includes the first receptor,
2) screening a library of second molecules for their ability to selectively bind to said first receptor of said first molecule,

3) isolating the members of the library that selectively binds in step 2, and
4) preparing, by means of synthesis or recombinant technology, the chimeric binding protein that contains at least a) the binding site of a member isolated in step 3, b) a scaffold protein structure autologous in the animal that stabilises the native 3D structure of said binding site, and c) a non-human MHC Class II binding amino acid sequence; or
I) preparing, by means of synthesis or recombinant technology, a chimeric binding protein containing 1) the second receptor or a mimotope thereof in correct, native 3D conformation, 2) a scaffold protein structure autologous in the animal, said scaffold protein structure stabilising said 3D conformation and being derived from another molecule in the animal than the second receptor, and 3) the tolerance breaking amino acid sequence.

41. The method according to claim 39 or 40, wherein the first molecule is an antibody, preferably a monoclonal antibody.

42. The method according to claim 41, wherein the first receptor is the idiotype of the antibody.

43. The method according to any one of claims 39-42, wherein the screening in step 3 includes an exclusion step that allows identification of members of the library that bind the first molecule outside the first receptor so as to exclude such members from subsequent steps.

44. The method according to claim 43, wherein said exclusion step involves
a) a test of the library members' ability to bind to the parts of the first molecule that are outside the first receptor, so as to allow exclusion of library members that exhibit such binding, and/or
b) a test of the library members' ability to compete with the second receptor for binding to the first receptor that allows exclusion of library members that do not exhibit such ability.

45. The method according to any one of claims 40-44, insofar as these are dependent on claim 40, wherein step 3 involves phage display of the second molecules.

46. The method according to any one of claims 40-44, insofar as these are dependent on claim 40, wherein step 3 involves that the library of second molecules is subjected to ribosome display, mRNA-display, or yeast surface display.

47. A method for down-regulating a self-antigen or a cell that displays epitopes of said self-antigen in an animal, the method comprising presenting the animal's immune system with an immunogenically effective amount of a chimeric binding protein according to any one of

claims 1-25 so as to induce a specific immune response against the self-antigen that includes in its structure the second receptor defined in claim 1 or 25.

48. The method according to claim 47, wherein an effective amount of the chimeric binding protein is administered to the animal via a route selected from the parenteral route such as the intracutaneous, the subcutaneous, and the intramuscular routes; the peritoneal route; the oral route; the buccal route; the sublinqual route; the epidural route; the spinal route; the anal route; and the intracranial route.

49. The method according to claim 48, wherein the effective amount is between 0.5 µg and 2,000 µg of the chimeric binding protein.

50. The method according to any one of claim 47-49, wherein the chimeric binding protein is contained in a virtual lymph node (VLN) device.

51. The method according to any one of claims 47-50, wherein the chimeric binding protein has been formulated with an adjuvant which facilitates breaking of autotolerance to autoantigens.

52. The method according to claim 47, wherein presentation of the chimeric binding protein to the immune system is effected by introducing nucleic acid(s) encoding the chimeric binding protein into the animal's cells and thereby obtaining in vivo expression by the cells of the nucleic acid(s) introduced.

53. The method according to claim 52, wherein the nucleic acid(s) introduced is/are selected from naked DNA, DNA formulated with charged or uncharged lipids, DNA formulated in liposomes, DNA included in a viral vector, DNA formulated with a transfection-facilitating protein or polypeptide, DNA formulated with a targeting protein or polypeptide, DNA formulated with Calcium precipitating agents, DNA coupled to an inert carrier molecule, DNA encapsulated in chitin or chitosan, and DNA formulated with an adjuvant.

54. The method according to claim 53, wherein the nucleic acid(s) is/are contained in a VLN device.

55. The method according to any one of claims 47-54, which includes at least one administration/introduction per year, such as at least 2, at least 3, at least 4, at least 6, and at least 12 administrations/introductions.

56. The method according to claim 47, wherein presentation to the immune system is effected by administering a non-pathogenic microorganism or virus which is carrying and expressing a nucleic acid fragment according to claim 26.